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Hormonal contraception: recent advances and controversies

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This document will outline new delivery systems and contraceptive formulations, summarize recent advances in emergency contraception, and review the effects of hormonal contraception on cancer risks, cardiovascular disease, and bone. (Fertil Steril® 2004;82(Suppl 1):26–32. ©2004 by American Society for Reproductive Medicine.)

The first hormonal contraceptive, Enovid™ (150 μg mestranol and 9.85 mg norethynodrel), was approved by the Food and Drug Administration (FDA) for use in the United States in 1960. Oral contraceptives (OCs) are now the most widely used reversible form of hormonal contraception in the United States. A wide variety of hormonal contraceptives are now available. Their mechanisms of action include inhibition of ovulation and/or modification of the endometrium, thus preventing implantation.

In addition to the contraceptive benefits, many other health benefits have been realized with hormonal contraception, including prevention of endometrial and ovarian cancers, control of menstrual bleeding, and relief from cyclic pelvic pain. In the evolution of OCs to their current forms, modifications have been made in efforts to decrease side effects and improve effectiveness and compliance. The first change was a decrease in the dose of estrogen and progestin, which led to the low dose formulations used today (1). Subsequently, new progestins were developed to decrease androgenic side effects. More recently, alternative delivery systems have been introduced in an effort to improve tolerability, compliance, and convenience; these delivery systems include transdermal, implantable, and injectable systems.

This document will outline new delivery systems and contraceptive formulations, summarize recent advances in emergency contraception, and review the effects of hormonal contraception on cancer risks, cardiovascular disease, and bone.

INJECTABLE COMBINED ESTROGEN/PROGESTIN CONTRACEPTION

The injectable combined estrogen/progestin contraceptive (Lunelle®) was approved by the FDA for use in the United States in 2000. This injectable contraceptive contains 25 mg of medroxyprogesterone acetate and 5 mg of estradiol cypionate (MPA/E_2C) and is administered by deep intramuscular injection every 23 to 33 days. The contraceptive efficacy is similar to depot medroxyprogesterone acetate (DMPA) and OCs, with an estimated failure rate of 0–0.1 per 100 woman-years (2, 3). The most common side effect reported is irregular bleeding during the first three months. Over the longer term, however, most women (83%) have regular menses when using this contraceptive (3, 4). Unlike the other injectable contraceptive DMPA, return to normal ovulatory cycles is rapid and occurs within 63 to 112 days after the final injection (5). MPA/E_2C therefore offers the advantage of an injectable form of contraception with less bleeding and faster return to fertility than DMPA and with a side-effect profile similar to OCs. The product has since been removed from the market and, at the time of this printing, its future was uncertain.

TRANSDERMAL HORMONAL CONTRACEPTION

The transdermal combined estrogen/progestin contraceptive patch (Ortho Evra™/Evra™)

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was approved by the FDA for use in the United States in 2002. The patch is 20 cm^2 (4 × 5 cm) and delivers 20 μg/d of ethinyl estradiol and 150 μg/d of norelgestromin (a biologically active metabolite of norgestimate) (6). The dosing is one patch weekly for three consecutive weeks, followed by a patch-free week. The patch may be applied to the buttock, abdomen, upper outer arm, or upper torso excluding the breasts. Mean serum concentrations of hormone are not affected by heat, humidity, exercise, or cold-water immersion (6). The observed contraceptive failure was 0.7 per 100 woman-years (95% CI, 0.31–1.10) but was higher in women with body weight >90 kg (7). The transdermal contraceptive is well tolerated and has a side effect profile similar to OCs (8).

CONTRACEPTIVE VAGINAL RING

A combined estrogen/progestin contraceptive vaginal ring (CVR) (NuvaRing®) was approved by the FDA for use in the United States in 2001. This contraceptive device consists of a flexible ring made of ethylene vinyl acetate copolymer with an outer ring diameter of 54 mm and a cross-sectional diameter of 4 mm. The vaginal ring releases approximately 120 μg of etonogestrel (a biologically active metabolite of desogestrel) and 15 μg of ethinyl estradiol per day (9). The CVR is used for three weeks continuously followed by a one-week ring-free period to allow for regular menstrual bleeding. The advantage for the user is that the CVR is not fitted. It is inserted and removed by the user and may or may not be removed for coitus. The most common side effects reported include headache (6.6%), leukorrhea (5.3%), and vaginitis (5.0%) (10). The failure rate in one study was 0.65 per 100 woman-years (95% CI, 0.24–1.41) (10).

LEVONORGESTREL-RELEASING INTRAUTERINE DEVICE

A levonorgestrel (LNG)-releasing intrauterine device (IUD) (Mirena®) was approved by the FDA for use in the United States in 2000. The first progesterone-releasing IUD (Progestasert®) was approved by the FDA in 1976 but was removed voluntarily from the market in 2001. The LNG-IUD is T-shaped with a steroid reservoir containing 52 mg of levonorgestrel mixed with polydimethylsiloxane, which controls the release rate of hormone. The LNG-IUD remains in place for five years. The LNG-IUD has a failure rate between 0 and 0.2 per 100 woman-years (11); the ectopic pregnancy rate is 0.02 per 100 woman years (12). Menstrual bleeding is decreased by 75% in LNG-IUD users and is attributed to the progestin-induced decidualization and suppression of the endometrium (13); 20% to 50% of users become amenorrheic within the first two years after insertion (14). Following removal, there is rapid return to normal fecundability with one-year life-table pregnancy rates of 89 per 100 for women less than 30 years of age (15).

IMPLANTABLE CONTRACEPTIVES

Norplant®, the first implantable contraceptive device, was approved by the FDA for use in the United States in 1990 and withdrawn from the market in 2002 due to complications associated with removal. This device contained 216 mg of levonorgestrel in six implantable rods to be removed after five years. Newer developments in implantable contraception are focusing on fewer implant rods and less androgenic progestins. Norplant® II (Jadelle®) has been approved by the FDA but is not yet marketed in the United States. This system contains two rods 4 cm in length with total dose of 150 mg of levonorgestrel for a three-year duration. The failure rate is 0.8 to 1.0 per 100 woman-years (16, 17). A newer single implant system not yet available (Implanon®) contains the progestin etonogestrel (a desogestrel metabolite having less androgenic activity than levonorgestrel). The carrier polymer, ethylene vinyl acetate, is more stable than the silastic material used in Norplant®.

Among newer implant delivery systems currently under development, biodegradable progestin implants in the form of rods and pellets have the advantage that the implant does not need to be removed (18).

EVOLUTION OF ORAL CONTRACEPTIVES

Oral contraceptive agents have been modified over time to limit estrogen and progestin dosage and decrease side effects. It has been established that progestin combinations with low dose estrogens (30–35 μg ethinyl estradiol) are effective with limited side effects. Lower dose estrogens (20 μg ethinyl estradiol) and newer progestins have subsequently been introduced.

Newer Progestins

The original progestins used in hormonal contraceptives were all derived from ethisterone, an orally active testosterone derivative. Removal of the carbon at C-19 position confers progestational activity, with some residual androgenic activity (19). These progestins are referred to as 19-nortestosterones and include norethindrone, norethynodrel, norethindrone acetate, ethynodiol diacetate, levonorgestrel, and norethindrone enanthate.

The newer progestins include norgestimate, desogestrel, and gestodene (not available in the United States). These progestins were designed to minimize androgenic side effects such as acne, hirsutism, nausea, and lipid changes while increasing progestational effects (19). Among the progestins available in the United States, norgestimate has the greatest progestational effect, and levonorgestrel is the most androgenic (19). The newest progestin, drospirenone, is an analogue of the aldosterone antagonist spironolactone and exhibits both progestational and antiandrogenic activity (20).

Oral Contraceptives Containing Less Than 30 μg Ethinyl Estradiol

Low dose OCs with 20 μg ethinyl estradiol were initially marketed for use in perimenopausal women. However, these low dose preparations have been shown to be effective contraceptive agents in women of reproductive age, with reported pregnancy rates ranging between 0.07–2.1 pregnancies per 100 woman-years of treatment (21). When compared with a 35 μg OC, the 20 μg OC has comparable cycle control and reduced symptoms of bloating and breast tenderness (22).

Extended OC Therapy

Monthly withdrawal bleeding for women using hormonal contraception has been the traditional prescribing method. Recently, however, this has been challenged and the use of extended hormonal use to delay or prevent menses has been evaluated. A randomized controlled study compared a traditional 28-day cycle to an extended 49-day cycle of a 30 μg ethinyl estradiol/300 μg norgestrel monophasic birth control regimen (23). The extended regimen resulted in fewer bleeding days, and no increase in mean spotting or abnormal bleeding episodes. There were no significant differences in other reported side effects such as headaches, weight gain, cramping, or breast tenderness. Similar results have been obtained with extended use of OCs containing 20 μg of ethinyl estradiol (24).

EMERGENCY CONTRACEPTION

Available hormonal emergency contraceptive (EC) regimens are effective when used within 72 hours of unprotected intercourse regardless of stage in menstrual cycle (25, 26). Either a combined estrogen/progestin regimen or a progestin-only treatment regimen may be used. Both regimens include two doses, the second administered 12 hours after the first. Their effectiveness appears to result primarily from an inhibition or delay of ovulation and neither appears to interrupt or disrupt an already established pregnancy. The recommended combined estrogen/progestin treatment regimen includes 100 μg of ethinyl estradiol and 1 mg of norgestrel or 0.5 mg of levonorgestrel. The progestin-only regimen involves a higher 0.75 mg dose of levonorgestrel.

There are two FDA-approved and dedicated products for emergency contraception: Preven™ (pill containing 50 μg of ethinyl estradiol and 0.25 mg of levonorgestrel; two pills taken 12 hours apart) and Plan B® (pill containing 0.75 mg of levonorgestrel; one pill taken 12 hours apart).

The effectiveness of the EC is determined by comparing the number of pregnancies observed following treatment to the expected number of pregnancies in the absence of treatment. In evaluating the combined EC, a meta-analysis involving over 3,000 patients observed a 74% reduction in the pregnancy rate, compared to the theoretical or expected pregnancy rate (27). Less information is available regarding the success of the progestin-only regimen. The World Health Organization conducted a randomized trial in 1,001 women comparing the progestin-only regimen to the combined regimen (28). The proportion of pregnancies prevented in the progestin-only and combined regimens was 85% and 57%, respectively, with the progestin-only regimen being significantly more effective (RR = 0.36; 95% CI, 0.18–0.70). However, it must be noted that the emergency contraceptive is still less effective in pregnancy prevention than consistent use of other contraceptive methods. Nausea and vomiting are the predominant side effects occurring in 42% and 16% of patients using the combined regimen, respectively (29), though these symptoms are significantly less with the progestin only regimen (28). Ectopic pregnancy can occur following emergency contraception, but the risk does not appear to be increased (30). There are no contraindications to the EC except pregnancy, although no studies have investigated outcomes in women with contraindications to combined OC (31). The progestin-only regimen may be a better choice for women with a personal or a family history of thrombosis.

Antiprogestins have been evaluated for use as emergency contraception. Mifepristone in a single dose of 600 mg, 100 mg, 50 mg, or 10 mg is equally effective in the prevention of pregnancy and has been shown to be more effective than the combined OC regimen with fewer side effects (32–34).

HORMONAL CONTRACEPTION AND CANCER RISK

Breast Cancer

Breast cancer is very rare in young women. The cumulative risk is less than 10 per 10,000 in women of all races up to age 35 years (35). Breast cancer risk associated with OC use has been evaluated in a pooled analysis from 54 studies involving 53,297 women with breast cancer and over 100,000 controls (36). The main finding was a small increase in the relative risk of localized breast cancer associated with current OC use (RR = 1.24; 95% CI, 1.15–1.33) and also with OC use within one to four years (RR = 1.16; 95% CI, 1.08–1.23), compared to controls. This risk declines shortly after stopping use and disappears within 10 years. By age 50, there is no difference in risk of breast cancer in ever users of OC and controls.

The study also demonstrated that breast cancers diagnosed in OC users were significantly less advanced than those in never users (for spread of disease beyond the breast, RR = 0.88; 95% CI, 0.81–0.95). Overall, there is no evidence of any increase in lifetime risk of breast cancer among OC users. Breast cancer risk associated with use of OC in perimenopausal women has not been evaluated.

Endometrial Cancer

Oral contraceptive use is associated with a lower risk of endometrial cancer. A meta-analysis found that the incidence

would be reduced by 56%, 67%, and 72% with use of combined OCs for four, eight, and 12 years ($P<0.0001$) (37). The lowered risk of disease persists after stopping OC use and by 20 years is almost 50% below that in women who have never used OCs (37).

When taken for more than 12 months, combined OCs confer equal protection against the three major histological subtypes of endometrial cancer: adenocarcinoma, adenosquamous carcinoma, and adenoacanthoma (38). Whereas earlier studies evaluated the effect of high dose OC preparations, a Swedish case–control study indicates that lower dose (30–35 μg) OC formulations provide comparable protection (39). DMPA has been shown to decrease the risk of endometrial cancer by 80%, with protective effects lasting for at least eight years after cessation of treatment (40).

Ovarian Cancer

The risk of ovarian cancer declines with increasing duration of OC use. The incidence is 41%, 54%, and 61% lower with use for four years, eight years, and 12 years, respectively ($P<0.0001$) (37). The protective effects of OCs become apparent after as little as three to six months of use and continue for up to 20 years after discontinuation (41, 42). The protective effect most likely derives from the progestin component of the combined OC (43). Risk for the four main histologic subtypes of epithelial ovarian cancer (serous, endometrioid, mucinous, and clear cell) is reduced to the same degree. Ovarian cancer risk associated with OCs containing the newer progestins, biphasic and triphasic pills, or lower dose OCs (20 μg ethinyl estradiol) has not yet been clearly defined but appears similar.

Oral contraceptives may also have protective benefits for women at risk for hereditary ovarian cancer (44). Continuous use for 10 years in women with a family history of ovarian cancer may reduce the risk of epithelial ovarian cancer to a level less than or equal to that observed in women with no family history of the disease (45). A case–control study involving 207 women with hereditary ovarian cancer (with BRCA1 and BRCA2 genetic mutations) and 161 of their sisters as controls found significant protection against ovarian cancer with any past use of OCs compared with never use (RR = 0.5; 95% CI, 0.3–0.8) (44). Greatest protection was noted with six or more years of use (RR = 0.3; 95% CI, 0.1–0.7).

Cervical Cancer

The use of OCs has been associated with an increased risk of cervical intra-epithelial neoplasia (CIN) and cervical cancer (41, 46–49). However, since the human papillomavirus (HPV) has been implicated as the main causative agent in cervical cancer (50), OC use most likely acts as a co-factor in the development of this disease (51). A recent study of pooled data from case–control studies of invasive cervical cancer (eight studies) and carcinoma in situ (two studies) evaluated the risk of cervical cancer in women who were using hormonal contraception and tested positive for the HPV (49). Hormonal contraception for fewer than five years did not increase the risk of cervical cancer (OR = 0.73; 95% CI, 0.52–1.03). However, risk increased with use of hormonal contraception for five to nine years (OR = 2.82; 95% CI, 1.46–5.42) and was greatest with use for 10 years or longer (OR = 4.03; 95% CI, 2.09–8.02). The proposed mechanism for this association is a hormonal effect on the cervix, a hypothesis that is supported by the increased risk of cervical cancer associated with increased parity and HPV (52) and the correlation between higher estradiol receptor concentrations induced by OCs and the risk of low-grade CIN (48).

Colorectal Cancer

There is growing epidemiologic evidence that OCs may protect women from developing colorectal cancer. In a meta-analysis, the overall estimated relative risk of colon cancer in OC users was 0.82 (95% CI, 0.74–0.92). The protection was stronger for women who had used OCs within the previous 10 years (RR = 0.46; 95% CI, 0.30–0.71) (53).

MEDICAL RISKS OF HORMONAL CONTRACEPTION

Hormonal Contraception and Bone Density

Depot-medroxyprogesterone acetate (DMPA) use has been associated with short-term bone loss in reproductive age women, an observation attributed to lower ovarian estrogen production resulting from suppression of gonadotropin secretion. Cross-sectional studies have demonstrated a decrease in bone density in the spine and distal radius in women currently using DMPA (54–56). Although bone loss correlates with duration of treatment and becomes significant after 15 years of use (57), other studies indicate the effect is reversible after discontinuation of treatment and therefore may not pose any longer term risk (55, 58, 59). Bone loss has also been documented in a small study of adolescent girls using DMPA; a 3% decrease in lumbar spine bone mineral was observed in users compared to a 9% increase in controls (60). These observations have raised legitimate concerns that DMPA use in adolescents may prevent them from achieving normal peak bone mass, although the contraceptive benefits of DMPA use in the adolescent population may outweigh any potential adverse effect on bone density.

The levonorgestrel-containing contraceptive implant has also been evaluated for its effect on bone density, although data are limited. A small study in seven adolescents showed a significant increase in lumbar spine bone density over 12 months (60). Studies of forearm bone density in adults have yielded conflicting results, with both increases and decreases reported (55, 61). The levonorgestrel implant should not decrease bone density as much as DMPA, because estrogen levels are not as consistently suppressed (18), and 19-norprogestogens have a beneficial effect on bone (62).

The effect of combination OCs on bone density is less clear. Studies in postmenopausal women who have previously used OCs have revealed improved bone density that correlates with years of use (63). Reduced fracture risks that correlate with the use of high-dose formulations and use after the age of 40 have also been demonstrated in postmenopausal women (64). Short-term studies in current users have demonstrated a small gain in bone density or no significant change (55, 56, 65). One small study suggested that gain in bone density over a 12-month period was greater with a norethindrone-containing OC compared to another containing desogestrel (56). However, no study has shown a detrimental effect of OCs on bone mass.

Myocardial Infarction

Myocardial infarction is extremely rare among reproductive aged women. The base line risk of myocardial infarction among healthy women rises from two per million at age 30 to 34 to 20 per million at age 40 to 44 (66). Use of low dose OCs increases the risk of myocardial infarction by approximately two-fold among users even after controlling for cardiovascular risk factors (including smoking, hypertension, hypercholesterolemia, diabetes, and obesity) (67). The myocardial infarction risk in OC users is increased by smoking, an effect that is more noticeable among women over age 35 years. For women under age 35, the incidence of myocardial infarction for smokers (35 per million) is increased 10-fold over that for nonsmokers (3 per million). For women over age 35, the risks of myocardial infarction are significantly higher for both smoking (40 per 100,000) and nonsmoking women (3 per 100,000) (68). Oral contraceptives should therefore be used with caution in women over age 35 who smoke.

Ischemic Stroke

Ischemic stroke too is very rare among healthy reproductive aged women. The annual incidence rises with increasing age (6 per million at age 20–24, 10 per million at age 30–34, and 16 per million at age 40–44) (66). A summary of five epidemiological, case–control studies involving 257 exposed cases estimated that the risk of ischemic stroke was 2.2-fold higher (95% CI, 1.9–2.7) with current use of OCs containing <50 μg ethinyl estradiol, compared to non-users. Risk is not related to the progestin component of OCs (69). Among women with a history of migraines, the relative risk of ischemic stroke is not significantly increased for those using OCs containing <50 μg ethinyl estradiol, compared to non-users (70, 71). The risk of ischemic stroke associated with OCs is not significantly different in women with simple migraine (no aura) compared to those with classic migraine (with aura) (70, 71). The risk of stroke in women with migraines who use OCs is increased significantly by smoking (70). Oral contraceptives should not be used in patients with visual changes or focal neurologic deficits associated with migraine headache (i.e., weakness, speech deficits).

Hemorrhagic Stroke

The incidence of hemorrhagic stroke among healthy women rises from 13 to 24 to 46 cases per million per year for ages 20 to 24, 30 to 34, and 40 to 44 years, respectively (66). In a review of three studies completed in the 1990s, the OC-associated risk of hemorrhagic stroke for users under 35 years of age was not increased compared to non-users (RR = 1.0, 95% CI, 0.7–1.5). For OC users ages 35 and older, the OC-associated risk of hemorrhagic stroke was 2.2-fold higher compared with non-users (95% CI, 1.5–3.3).

Venous Thromboembolism

The incidence of venous thromboembolism (VTE) among healthy women is low but increases with age from 32 to 46 to 59 cases per million per year for ages 20 to 24, 30 to 34, and 40 to 44 years, respectively (66). Oral contraceptive use is associated with a three-fold higher risk of VTE (66). The risk appears to be proportional to the estrogen dose (72). However, studies have also suggested that the risk of VTE is less than two-fold higher for OC formulations containing the newer progestins (desogestrel and gestodene compared to levonorgestrel (73). A meta-analysis including three cohort and nine case–control studies of VTE risk associated with newer progestins yielded an overall adjusted odds ratio (OR) for VTE of 1.7 (95% CI, 1.4–2.0) with an absolute excess risk of 1.5 events per 10,000 woman-years for women using formulations containing desogestrel or gestodene (74). The risk remained significantly elevated for short-term and long-term users and for users of differing ages but is far less than that associated with pregnancy. Although the risk of VTE is statistically significant, it is still a rare event and would translate to one to two cases per 10,000 women years of use (75). The FDA has suggested no change in prescribing (57).

The risk of VTE associated with prothrombotic conditions is further increased with OC use. The most common of these is the Factor V Leiden mutation which results in resistance to activated protein C. The risk of VTE in women who are heterozygous for the mutation is seven-fold higher than in non-carriers. In women who are heterozygous carriers and use OCs, the risk is 35-fold higher (95% CI, 7.8–154) (76). The prevalence of the Factor V Leiden mutation is 5% in Caucasians but extremely low in Asian and African populations (77). A genetic defect in prothrombin is also associated with increased risk of VTE and increases the risk of VTE in users of OCs (78). Other known factors involved in the development of VTE include protein C, protein S, and antithrombin III deficiencies (76). The presence of more than one of these mutations increases the risk of VTE significantly. Oral contraceptives should not be used in individuals who carry these mutations. At this time, screening for these mutations prior to initiating OC use is recommended only for women having a personal or family history of thrombosis (76).

CONCLUSIONS

- Hormonal contraception is a safe and effective form of reversible contraception.
- New transdermal, injectable, vaginal, and implantable delivery methods appear to have safety and efficacy comparable to that of OCs.
- Modifications of OCs, including progressively lower doses of estrogens and the development of newer progestins, have maintained contraceptive efficacy while reducing the incidence of side effects.
- Emergency contraception using either combined estrogen/progestin or progestin-only regimens is effective in reducing the risk of pregnancy. The progestin-only regimen may be more effective with fewer side effects.
- There is a reduced incidence of endometrial and ovarian cancers in past and current users of OCs.
- There is a potential for increased risk of cervical cancer with longer durations of OC use.
- There is no increase in lifetime risk of breast cancer associated with OC use, although prevalence is modestly increased in the first five years of use.
- The risk of stroke and myocardial infarction in reproductive aged women is low, but is increased in OC users over age 35 who smoke.
- The risk of VTE is increased in OC users and higher in those heterozygous for mutations resulting in prothrombotic conditions. At this time, screening for thrombophilias prior to initiating therapy with OCs is recommended only for women having a personal or a family history of thrombosis.

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